Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Palliative Care Improves Quality for the Seriously Ill

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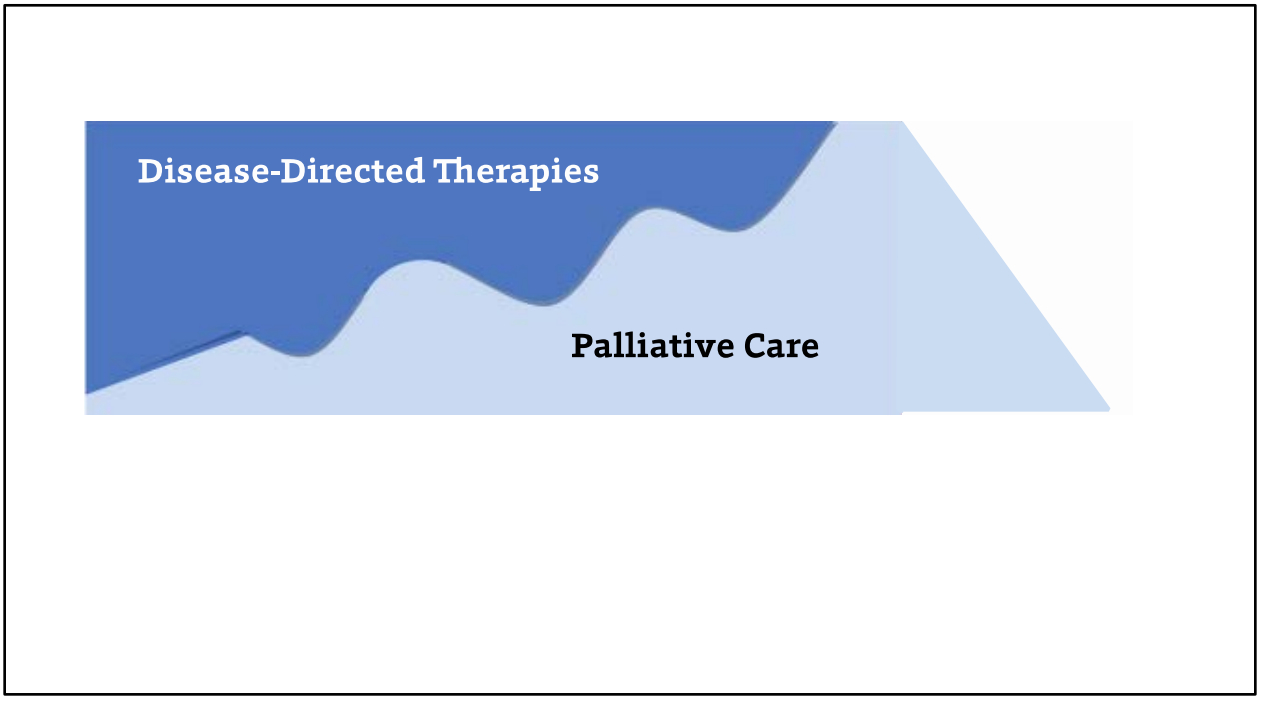
Figure S1. Integration of Palliative Care over the Course of Serious Illness



Modern medicine offers therapies for serious illness that are predominantly disease modifying, and in limited cases, potentially curative. These disease-directed treatments begin at the time of diagnosis, when symptom management and other palliative care needs are usually limited. Throughout the course of illness palliative care needs typically increase and often wax and wane over time. Late in this trajectory, palliative care may be the primary or sole focus of one's care plan. After death, bereavement counseling and support of surviving family and friends continues.

Table S1. Management of Common Symptoms in the Setting of Serious Illness*

Symptom	Special Considerations	Specific treatments
Anorexia and cachexia	1. Frequent early sign of serious illness; 2. As metabolic abnormalities exist prior to overt weight loss, we recommend initiating treatment at pre-cachexia phase (presence of serious illness, systemic inflammatory response, unintentional low-grade weight loss (<=5% within 6 months) pending definitive controlled clinical trials; 3. Screening for distress related to eating/ altered body image and provision of psychological support are indicated in the setting of refractory cachexia.	1. Oral intake: broad balanced diet with increased protein to maintain diminished skeletal muscle mass 2. Exercise: Critical to counteract muscle wasting 3. Anti-inflammatories: Preliminary evidence supports 1.5-2 g of eicosapentaenoic acid daily for retention of lean body mass 4. Appetite stimulants (corticosteroids and progestational agents) increase food intake and weight but the effects are short-lived and have limited long-term benefits on quality of life and no survival benefits
Anxiety	1. Many patients may not express anxiety directly. Listening for key words "concerned", "scared", "worried", "nervous" is helpful in eliciting experiences of anxiety or fear 2. Anxiety may be lessened by explicit expressions of empathy, such as, "It must be frightening to hear this news" or "What worries you the most?".	1. Non pharmacological interventions are particularly effective for mild-moderate anxiety and can include psychotherapy; integrative therapies (music, mindfulness, relaxation); and exercise 2. Selective serotonin reuptake inhibitors (SSRI) are standard of care in the medically well but time to efficacy of several weeks may limit their use in the seriously ill. Gabapentin or Trazadone are often effective alternatives to standard treatments. In cases where anxiety is acute and immediate relief required, short acting benzodiazepines (e.g., lorazepam) can be employed, while a long-acting formulation (e.g., clonazepam) may be needed if anxiety is chronic.
Constipation	1. Most common symptom in the seriously ill. 2. Nearly universal in patients taking opioids. Unless contraindicated, prophylactic laxatives are indicated when initiating opioid therapy	1. No randomized trials document superiority of one standard laxative over another and recommendations that follow are based on consensus opinion and best practice. 2. Begin with escalating doses of a bowel stimulant (i.e., senna) and if dose escalation

		is ineffective, add an osmotic agent. If ineffectual, consider disimpaction or suppositories or enemas 3. Docusate sodium alone has been shown to be ineffectual and should only be used in combination with laxatives 4. In cases of refractory opioid-related constipation, methylnaltrexone may be considered
Depression	1. Common in setting of serious illness with prevalence rates as high as 42% in palliative care settings. 2. Optimal support and effective communication may help prevent symptoms of depression. 3. Somatic symptoms are not reliable indicators of depression in the setting of serious illness. 4. Query patients as to presence of feelings of helplessness, hopelessness, anhedonia, loss of self-esteem, worthlessness, persistent dysphoria, and suicidal ideation.	1. Cognitive behavioral therapy appears to offer considerable benefit. Data are more mixed and less supportive of social support and family interventions 2. For pharmacological therapies, base treatment on expected prognosis, if greater than 6 months, use standard therapies (e.g., SSRI). If less than 6 months, strongly consider use of psychostimulants given their rapid onset of action. 3. Tricyclic antidepressants are relatively contraindicated because of side effects. 4. Non-pharmacological interventions, including exercise may benefit mood.
Delirium	1. Extremely common as death approaches 2. Seek to identify reversible conditions	1. Identify and address underlying causes 2. Behavioral therapies, including: avoidance of excess stimulation; frequent reorientation, and reassurance; and presence of caregivers, are often extremely effective 3. Haloperidol remains pharmacological therapy of choice; chlorpromazine can be used for agitated or terminal delirium 4. Benzodiazepines may exacerbate delirium and should be avoided, except when needed in terminal delirium.
Dyspnea	1. Seek to identify reversible conditions	1. Oxygen found to be beneficial in setting of hypoxia associated dyspnea. In absence of

		hypoxia, room air – delivered by hand-held fan or via nasal cannula reduces breathlessness through stimulation of V2 branch of trigeminal nerve. 2. Opioids remain first-line therapy for breathlessness and act without measurable reductions in respiratory rate or oxygen saturation; effective doses are often lower than those used to treat pain. 3. Non-pharmacological interventions, including pulmonary rehabilitation, non-invasive ventilation, and others may provide benefit. 4. Nebulized opioids have not been shown to be efficacious in controlled trials
Fatigue	1. Most common and distressing symptom in setting of serious illness	1. Behavioral modifications that are energy-conserving are the main stay of therapy. 2. Non-pharmacological interventions, including exercise and rehabilitation programs. 3. Psychostimulants may be considered in select cases, However pharmacologic interventions are poorly studied in the seriously ill population
Nausea/Vomiting	1. Determine underlying mechanism(s) [e.g., direct stimulation of the chemoreceptor trigger zone (D_2, 5-HT3, NK1 receptors), stimulation of chemo/mechanoreceptors in the gi tract (5=HT3), vestibular stimulation (Achm, $H_{1,}$)] and select agent based on likely mechanism/active receptor type	1. Prior to initiating pharmacologic therapy, assess for and eliminate environmental stimuli. 2. Select agent based on likely pathway (e.g., odansetron for 5-HT3 mediated nausea, metoclopramide for D_2 mediated nausea) 3. Consider steroids to reduce tumor edema in setting of either cortical nausea or visceral organ involvement. 4. Consider pro-kinetics for opioid and non-opioid related delayed gastric emptying
Pain	1. Opioids remain the agent of choice for most pain syndromes. Non-steroidal anti-	1. Medications to be administered on a standing or regular basis. Begin with short

	inflammatory medications or acetaminophen can be used for mild-moderate pain although most patients with serious illness will require opioids for pain. 2. Initiate a regimen to prevent constipation for all patients receiving opioids. 3. Pain from bone metastastes may be treated with radiation therapy, intravenous bisphosphonates, NSAIDs or corticosteroids. 4. Interventions, such as regional nerve blocks, may be used in select cases of cancer-related pain.	acting formulations and convert to extended release or transdermal preparations once pain is well controlled and opioids are at steady state 2. As-needed or rescue doses should be available for breakthrough pain or pain not controlled by the standing regimen. As needed doses are set at 10% of the total daily doses and administered every 15 to 60 minutes as needed. 3. Pain emergencies (crisis) should be managed with rapid boluses (every 15 minutes) of intravenous opioids (5-10 mg of morphine sulfate equivalents for an opioid naïve patient) 4. Patients with neuropathic pain syndromes may benefit from single agent therapy with anti-convulsants (pregabalin, gabalin), tricyclic antidepressants, topical lidocaine, or combination therapy with opioids

*For details of recommendations and more information about the management of symptoms, see references [1-5]. Where data are lacking, recommendations are based upon consensus opinion and best practices.

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